



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61K 31/35, 31/40, 31/225	A1	(11) International Publication Number: WO 95/13063 (43) International Publication Date: 18 May 1995 (18.05.95)
(21) International Application Number: PCT/US94/13068 (22) International Filing Date: 9 November 1994 (09.11.94) (30) Priority Data: 149,252 9 November 1993 (09.11.93) US (71) Applicants: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). THE BRIGHAM AND WOMEN'S HOSPITAL, INC. [US/US]; 75 Francis Street, Boston, MA 02115 (US). EMORY UNIVERSITY [US/US]; 1440 Clifton Road N.E., Room 116, The Whscab Building, Atlanta, GA 30322 (US). (72) Inventors: HIRSCH, Laurence J., III; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). BOCCUZZI, Stephen, J.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). PLOTKIN, Diane, J.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MITCHEL, Yale, B.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). GANZ, Peter; 75 Francis Street, Boston, MA 02115 (US). CREGGER, Mark, A.; 75 Francis Street, Boston, MA 02115 (US). ALEXANDER, R., Wayne; 1440 Clifton Road N.E., Room 116, The Whscab Building, Atlanta, GE 30322 (US).		(74) Common Representative: MERCK & CO., INC.; Patent Dept., 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ). Published <i>With international search report.</i>
(54) Title: HMG-CoA REDUCTASE INHIBITORS IN THE NORMALIZATION OF VASCULAR ENDOTHELIAL DYSFUNCTION		
(57) Abstract <p>Treatment of patients with or at risk of developing ischemic syndromes with doses of an HMG-CoA reductase inhibitor to lower total and LDL cholesterol in order to restore endogenous vascular endothelium-dependent activities including, but not limited to vasodilatory responses modulating vascular tone and blood flow, anti-adherent properties of the blood vessel wall and anti-coagulation of platelets.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
RJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LJ	Liechtenstein	SN	Senegal
CN	China	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
CZ	Czech Republic	LV	Latvia	TJ	Tajikistan
DE	Germany	MC	Monaco	TT	Trinidad and Tobago
DK	Denmark	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	US	United States of America
FI	Finland	ML	Mali	UZ	Uzbekistan
FR	France	MN	Mongolia	VN	Viet Nam
GA	Gabon				

- 1 -

TITLE OF THE INVENTIONHMG-CoA REDUCTASE INHIBITORS IN THE NORMALIZATION
OF VASCULAR ENDOTHELIAL DYSFUNCTION5 BACKGROUND OF THE INVENTION

The vascular endothelium which lines the blood vessels is a widely distributed organ interposed between the intravascular and extravascular spaces. It has many functions in the regulating vessel diameter, varying blood flow, maintaining of vascular homeostasis, and the vascular response to injury. In the normal basal physiological state the endothelium provides a nonthrombotic, noninflammatory vascular lining. Endothelial cells respond to potential harmful conditions (mechanical stress, anoxia, ischemia and oxidative stress) and a variety of hormones and vasoactive mediators by inducing coagulation and production of inflammatory mediators through the production of bioactive compounds.

The vascular endothelium plays a critical role in mediating primarily vasodilation, but also vasoconstriction. In response to vasoactive stimuli such as acetylcholine (ACh), ATP, ADP, bradykinin, arachidonic acid, histamine, thrombin, serotonin, and substance P, the endothelium produces and releases a highly labile substance called endothelium-derived relaxing factor (EDRF). EDRF is believed to be nitric oxide (designated EDRF-NO) and is synthesized from L-arginine. EDRF mimics nitroglycerine by stimulating guanylate cyclase in vascular smooth muscle resulting in an increase in cyclic GMP and subsequent relaxation. Studies in which the formation of EDRF is inhibited by N^ω-monomethyl-L-arginine (L-NMMA) indicate that the endothelium continuously releases EDRF to regulate basal vascular tone. Thus, the endothelium mediates both acute changes in local blood flow as well as ambient regulation of blood pressure.

Risk factors for the development of atherosclerosis such as high blood pressure, smoking, diabetes, hyperlipidemia and hypercholesterolemia have been related to abnormal responses by the vascular endothelium to secrete EDRF which normally functions to dilate

- 2 -

the blood vessel. Under normal physiological conditions, the endogenous dilator secreted by the vascular endothelium causes relaxation of the underlying smooth muscle in the blood vessel and dilation of the blood vessel. The normal state of the cardiovascular system is one of active vasodilation dependent on the continuous generation of NO by the vascular endothelium. In the absence of the endogenous vasodilator, the blood vessels constrict, resulting in a decrease in the blood supply. These effects may contribute to the production of ischemic syndromes such as angina pectoris, myocardial infarctions, coronary artery disease (CAD), hypertension, cerebrovascular accidents, transient ischemic attacks, chronic obstructive pulmonary disease, chronic hypoxic lung disease, pulmonary hypertension, renal hypertension, chronic renal disease, microvascular complications of diabetes and vasoocclusive complications of sickle cell anemia.

Several pathological conditions impair endothelium-dependent vasodilation. Atherosclerosis reduces endothelium-dependent relaxation *in vitro* and *in vivo* in arteries from animals fed high cholesterol diets (Friedman et al. *Circ. Res.* 58:783-789, 1986) and in humans with atherosclerotic coronary artery disease (Forstermann et al., *Circ. Res.* 62:185-190, 1988, and Zieher et al. *Circ.* 83:391-401, 1991). Hypercholesterolemia also causes abnormalities in vascular function; these may predate the development of atherosclerosis. Specifically, hypercholesterolemia impairs endothelium-dependent vasodilation *in vitro* and *in vivo*. Vascular endothelial dysfunction in a setting of hyperlipidemia in the human forearm has recently been described (Creager et al. *J. Clin. Invest.* 86:228-234, 1990). The contribution made by the endothelium to the regulation of vascular tone varies among different vascular beds and test animals.

The vascular beds are physically separate entities. The importance of ischemic spasm in different vascular beds may vary.

Wada et al. (*Am. J. Hematology* 44: 112-116, 1993) have conducted a study with pravastatin in patients with hypercholesterolemia, in which they postulate that since pravastatin significantly reduced plasma levels of plasminogen activating inhibitor 1 (PAI-I) and

- 3 -

thrombomodulin (TM), it is possible that it might ameliorate vascular endothelial cell injury. The reference focused on the coagulation aspects of vascular endothelial function and not the spastic function of the vascular endothelium. It is suggested that amelioration of hypofibrinolysis might produce a reduction in vascular endothelial cell markers.

Research is ongoing to develop noninvasive diagnostic tests to detect vascular endothelial dysfunction. The pathophysiological relationship between abnormal vascular endothelium-dependent response and clinical symptoms of both chronic and acute myocardial ischemia is also under investigation.

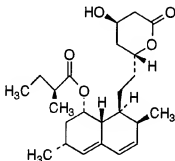
One diagnostic agent used to measure endothelial dysfunction is acetylcholine (ACh). Muscarinic receptors for ACh are present on both vascular endothelial and smooth muscle cells. In the presence of an intact endothelium, infusion of ACh stimulates EDRF release and relaxes the underlying smooth muscles causing vasodilation. However, when the endothelial function is abnormal, ACh paradoxically produces vasoconstriction due to an unopposed, direct reflection on the vascular smooth muscle. ACh constricts human atherosclerotic epicardial vessels because the vascular endothelium is dysfunctional in those arteries. Although it is unlikely that ACh plays a major role in the regulation of vascular tone *in vivo* (because most blood vessels lack cholinergic innervation), ACh is a reliable and sensitive test agent for evaluating the normal endothelial cell function and the capacity of the vascular endothelium to cause vasodilation.

Currently, angina due to myocardial ischemia is treated with chronic administration of vasodilators such as long-acting nitrates, sydnone derivatives, calcium channel blockers, β -blockers, and/or use of short-acting nitrates. These therapies have the drawbacks of the development of tolerance to the pharmacologic agents and/or the development of rebound effects. Furthermore, when effective, these vasodilators produce a basal state of vasodilation, and at times of increased demand, such as exercise or emotional stress, these agents are ineffective and may hinder acute responses to stimuli. These therapeutic

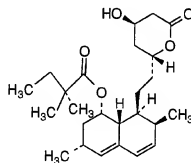
- 4 -

approaches treat only one aspect of endothelial dysfunction and do not normalize vascular endothelium function, as does the method of treatment of the present invention. The present invention improves and augments all endogenous functions served by the endothelium.

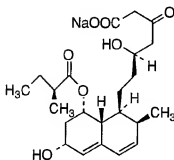
HMG-CoA reductase inhibitors are known to function as antihypercholesterolemic agents. They reduce hepatic cholesterol biosynthesis by inhibiting the enzyme HMG-CoA reductase which catalyzes the early, rate-limiting step in the biosynthesis of cholesterol, the conversion of hydroxymethylglutarate to mevalonate. Commercially available HMG-CoA reductase inhibitors include MEVACOR® (lovastatin), ZOCOR® (simvastatin), and PRAVACHOL® (pravastatin). The HMG-CoA reductase inhibitor fluvastatin has recently been approved in some markets.



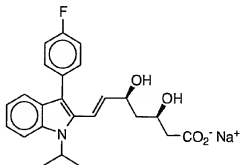
LOVASTATIN



SIMVASTATIN



PRAVASTATIN



FLUVASTATIN

- 5 -

Lovastatin and simvastatin are administered in the form of the lactone prodrugs shown above which are hydrolyzed in the liver to the active open β -hydroxyacid form.

Osborne et al. (*J. Clin. Invest.* **83**: 465-473, 1989) and
5 Harrison et al. (*J. Clin. Invest.* **80**: 1808-1811, 1987) report that rabbits and monkeys show improvement in vascular endothelial responsiveness to vasodilatory stimuli following lowering of serum cholesterol. However, the literature in animal models concerning this subject is highly
10 variable: different species and different vascular beds show variable levels of abnormality and recovery. Therefore, while it is encouraging to see positive results in animals, these results are not predictive of the response in humans.

Rutschmann et al. (1992) demonstrated that a reduced post
15 ischemic blood flow response in the human radial artery observed in patients with hypercholesterolemia was restored to normal following two years of treatment with simvastatin (between group comparisons only).

Leung et al., (*Lancet* **341**: 1496-1500, 1993) found that
20 treatment with diet and cholestyramine improved coronary endothelium-dependent relaxation in patients with angiographically normal arteries.

DETAILED DESCRIPTION OF THE INVENTION

The novel method of treatment of this invention comprises the administration to a patient at risk of developing atherosclerosis or a
25 patient in whom the disease has been diagnosed with an HMG-CoA reductase inhibitor to restore endogenous vascular endothelium dependent activities including improving the normal dilation capacity of the endothelium. This method may be used to induce vasodilation to modulate vascular tone and blood flow. Other improvements in vascular
30 endothelium dependent activities include decreasing the adherent properties of the blood vessel walls and decreasing the coagulation of platelets. Suitable subjects for the method of the present invention include those individuals who currently exhibit symptoms of atherosclerosis and those who are at risk of developing various acute ischemic syndromes including individuals with high blood pressure,

- 6 -

diabetes or hyperlipidemia, and individuals who smoke. Current efforts to develop non-invasive (ultrasound detection) methods to assess endothelial function will potentially identify other patients at risk.

5 The various acute ischemic syndromes that may be treated by the method of the present invention include: angina pectoris, coronary artery disease (CAD), hypertension, cerebrovascular accidents, transient ischemic attacks, chronic obstructive pulmonary disease, chronic hypoxic lung disease, pulmonary hypertension, renal hypertension, chronic renal disease, microvascular complications of diabetes and vasoocclusive
10 complications of sickle cell anemia.

 The HMG-CoA reductase inhibitor for use in the novel method may be selected from lovastatin, simvastatin, pravastatin and fluvastatin, preferably lovastatin or simvastatin, most preferably
15 lovastatin.

 The doses of HMG-CoA reductase inhibitor contemplated for use in this invention are about 5 to 80 mg per day preferably given in single or divided doses.

 Preferably, the patient is placed on a prudent lipid-lowering
20 diet during the treatment with the HMG-CoA reductase inhibitors.

 Lipid lowering therapy with HMG-CoA reductase inhibitors normalizes vascular function in patients with hypercholesterolemia and/or coronary artery disease without the requirement for significant regression of the atherosclerotic lesions. The coronary microcirculation, which demonstrates significantly impaired endothelium dependent
25 dilatory responses in the presence of hypercholesterolemia and atherosclerotic disease, but is usually free of atheroma, is likely to show marked improvement demonstrating the ability of lipid lowering therapy to halt the progression and/or promote regression of atherosclerosis in epicardial arteries in humans.

30 The following example is given for the purpose of illustrating the present invention and shall not be construed as being limitations on the scope or spirit of the invention.

- 7 -

EXAMPLE 1

Twenty three patients undergoing angioplasty in the Lovastatin Restenosis Trial were entered into a double-blind randomized 4-site study. Each patient received either 40 mg lovastatin twice a day or a placebo beginning 7 to 10 days before the angioplasty and continuing 6 months after the angioplasty.

Each patient was infused for 2 minutes each with acetylcholine (ACh, an endothelial dependent agent) at 10^{-9} M, 10^{-8} M, 10^{-7} M, 10^{-6} M, and with Nitroglycerin (NTG, an endothelial independent agent) at 40 micrograms for 2.5 minutes. The mean lumen diameter change between treatment groups was compared after ACh and NTG infusions at 7-10 days and at 6 months.

Results:Maximum Response to ACh (mean % change in lumen diameter)

Duration	<u>average of all segments</u>			<u>most constricting segment</u>		
	Pbo %	Lova %	p	Pbo %	Lova %	p
7-10 days (n=23)	-10	-9	N.S.	-27	-30	N.S.
6 months (n=19)	-13	-2	0.04	-19	-3	0.007

The response to nitroglycerin was unaffected by the treatment.

Although the study above has no true baseline, the following conclusions may be drawn from the data. First, both the lovastatin and placebo groups were similar at 7 to 10 days for both the average and most constricting segments. Second, at 6 months there was less constriction in the lovastatin group compared to the placebo for the average of all five

- 8 -

segments per vessel and in the most constricting segment in that vessel. The within group differences for the lovastatin group was marginally significant for all segments and significant for the most constricting segment ($p=0.04$).

5 While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the casual variations, adaptations, modifications, deletions, or additions of procedures and protocols described herein, as
10 come within the scope of the following claims and its equivalents.

15

20

25

30

WHAT IS CLAIMED IS:

1. A method of restoring endogenous vascular endothelium dependent activities selected from: preventing coagulation
5 of platelets, decreasing the adherent properties of blood vessel walls, and inducing vasodilation to modulate vascular tone and blood flow, which comprises the administration, to a human patient at risk of developing atherosclerosis or a patient with atherosclerosis of a therapeutically effective dose of a HMG-CoA reductase inhibitor.
10
2. The method of Claim 1 wherein the HMG-CoA reductase inhibitor is lovastatin, simvastatin, pravastatin or fluvastatin.
3. The method of Claim 2 wherein the dose of HMG-CoA reductase inhibitor is about 5 to 80 mg/day.
15
4. The method of Claim 3 wherein the HMG-CoA reductase inhibitor is lovastatin or simvastatin.
20
5. The method of Claim 4 wherein the HMG-CoA reductase inhibitor is lovastatin.
6. The method of Claim 5 wherein the dose of lovastatin
25 is 10 to 80 mg per day.
7. The method of Claim 6 wherein the dose of lovastatin is 80 mg per day.
8. The method of Claim 4 wherein the HMG-CoA reductase inhibitor is simvastatin.
30
9. The method of Claim 8 wherein the dose of simvastatin is 5 to 40 mg per day.

- 10 -

10. The method of Claim 9 wherein the dose of simvastatin is 40 mg per day.

5 11. The method of Claim 1 wherein the patient is at risk of developing atherosclerosis.

12. The method of Claim 1 wherein the patient has atherosclerosis.

10 13. The method of Claim 1 to prevent coagulation of platelets.

14. The method of Claim 1 to decrease the adherent properties of blood vessel walls.

15 15. The method of Claim 1 to induce vasodilation to modulate vascular tone and blood flow.

20 16. The method of Claim 1 which additionally comprises placing the patient on a lipid-lowering diet.

17. A method of preventing diseases associated with endothelial dysfunction selected from:

- 25 (a) angina pectoris,
(b) myocardial infarctions,
(c) coronary artery disease,
(d) hypertension,
(e) cerebrovascular accidents,
(f) transient ischemic attacks,
30 (g) chronic obstructive pulmonary disease,
(h) chronic hypoxic lung disease,
(i) pulmonary hypertension,
(j) renal hypertension,
(k) chronic renal disease,

- 11 -

(l) microvascular complications of diabetes, and
(m) vasoocclusive complications of sickle cell anemia
which comprises the administration to a human patient of a
therapeutically effective dose of an HMG-CoA reductase inhibitor.

5

18. The method of Claim 17 wherein the dose of the
HMG-CoA reductase inhibitor is from 5 to 80 mg per day.

10

19. The method of Claim 18 wherein the HMG-CoA
reductase inhibitor is selected from lovastatin and simvastatin.

20 The method of Claim 19 which additionally comprises
placing the patient on a lipid-lowering diet.

15

21. A method of treating diseases associated with
endothelial dysfunction selected from:

20

- (a) angina pectoris,
- (b) myocardial infarctions,
- (c) coronary artery disease,
- (d) hypertension,
- (e) cerebrovascular accidents,
- (f) transient ischemic attacks,
- (g) chronic obstructive pulmonary disease,
- (h) chronic hypoxic lung disease,
- (i) pulmonary hypertension,
- (j) renal hypertension,
- (k) chronic renal disease,
- (l) microvascular complications of diabetes, and
- (m) vasoocclusive complications of sickle cell anemia

25

30

which comprises the administration to a human patient of a
therapeutically effective dose of an HMG-CoA reductase inhibitor.

22. The method of Claim 21 wherein the dose of the
HMG-CoA reductase inhibitor is from 5 to 80 mg per day.

- 12 -

23. The method of Claim 22 wherein the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin.

5 24. The method of Claim 23 which additionally comprises placing the patient on a lipid-lowering diet.

10

15

20

25

30

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/13068**A. CLASSIFICATION OF SUBJECT MATTER**IPC(6) :A61K 31/35, 31/40, 31/225
US CL :514/460,419,548

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/460,419,548

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Extra Sheet.**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A, 3,983,140 (ENDO ET AL) 28 SEPTEMBER 1976, ENTIRE DOCUMENT.	1-24
A	US,A, 4,231,938 (MONAGHAN ET AL) 04 NOVEMBER 1980, ENTIRE DOCUMENT.	1-24
A	US,A, 4,346,227 (TERAHARA ET AL) 24 AUGUST 1982, ENTIRE DOCUMENT.	1-24
A	US,A, 4,448,784 (GLAMKOWSKI ET AL) 15 MAY 1984, ENTIRE DOCUMENT.	1-24
A	US,A, 4,450,171 (HOFFMAN ET AL) 22 MAY 1984, ENTIRE DOUCMENT.	1-24
A	US,A, 5,130,333 (PAN ET AL) 14 JULY 1992, ENTIRE DOCUMENT.	1-24

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	*A* document member of the same patent family

Date of the actual completion of the international search
19 DECEMBER 1994Date of mailing of the international search report
11 JAN 1995Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231Authorized officer
DEBORAH LAMBIN

Facsimile No. (703) 305-3230

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/13068

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A, 0,457,514 (BERGEY ET AL) 21 NOVEMBER 1991, ENTIRE DOCUMENT.	1-24
Y	Coronary Artery Disease, Vol. 2(5), issued July 1991, Siegfried et al, "Amelioration of coronary vascular endothelial...inhibitor lovastatin", see pages 621-627.	1-24
Y	Circulation Research, Vol. 58 (6), issued June 1986, Freiman et al, "Atherosclerosis Impairs Endothelium....in Primates", see pages 783-789.	1-24
Y	American Journal of Hematology, Vol. 44, issued 1993, Wada et al, "Elevated Plasma Levels of Vascular... Hypercholesterolemia", see pages 112-116.	1-24
Y	Scand. J. Clin. Lab. Invest., Vol. 50, issued 1990, Luscher, "Functional Abnormalities of the Vascular Endothelium...Atherosclerosis", see pages 28-32.	1-24
Y	The Lancet, Vol. 341, issued 12 June 1993, Leung et al, "Beneficial effect of cholesterol-lowering therapy....in hypercholesterolaemic patients ", see pages 1496-1500.	1-24

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/13068

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

CAS ONLINE

search terms: HMG-CoA reductase inhibitors/lovastatin, simvastatin, pravastatin, fluvastatin and cholesterol, atherosclerosis, coronary diseases, hypertension, ischemia, lipids